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A PRESCRIPTION TO REMEDY GLOBAL AGRICULTURAL ANTIBIOTIC RESISTANCE: AN
INTEGRATED APPROACH

by

Valerie Drake

A thesis submitted in partial fulfillment of the requirements
for graduation with Honors in the International Studies

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All requirements for graduation with Honors in the
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A PRESCRIPTION TO REMEDY GLOBAL AGRICULTURAL ANTIBIOTIC RESISTANCE: AN INTEGRATED APPROACH

Student Researcher: Valerie Drake
Faculty Mentor: Professor David Osterberg



University of Iowa College of Liberal Arts and Sciences
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Abstract

This study focuses on determining an effective public health policy strategy to address agricultural antibiotic resistance. The research examines domestic and international examples of governmental regulation, including the Food and Drug Administration's regulatory release, Guidance for Industry #213 (FDA GFI #213), which concerns the use of antibiotics in industrial livestock farming in the United States, and the contrasting Danish policy and surveillance techniques. To determine the effectiveness of voluntary measures, this research assesses motivations leading to the creation of FDA GFI #213 by referencing specific legal disclaimers, document audience, and enforcement methods. Taking these results, the study cross-examines the goals of FDA GFI #213 with annual FDA reports on rates of agricultural antibiotic use from 2009 through 2016. This study concludes that FDA GFI #213 has not contributed to a significant decline in agricultural antibiotic use. Therefore, voluntary regulation alone is thus far shown to be ineffective in confronting antibiotic resistant pathogens. A combination of mandatory and voluntary policies has been proven successful through the Danish method of precise surveillance and mandatory regulation. This study intends to contribute to the ongoing debate on policy approaches in combatting the proliferation of antibiotic resistance a culmination of industrial agriculture farming practices, legislation, and global human health.

Significance of Research

The significance of this study rests in its focus on the ever-growing threat of antibiotic resistance to global human and animal health. In recognition of the critical state of antibiotic overuse in agriculture, in 2016, the Expert Commission on Addressing the Contribution of Livestock to the Antibiotic Resistance Crisis developed eleven recommendations necessary for constructive progress (see graphic 1) (Expert Commission). George Washington University Milken Institute School of Public Health (GWSPH) and the Natural Resources Defense Council helped to organize and endorse the Commission, which is made up of twelve antibiotic-resistance specialists, including infectious diseases physicians, veterinarians, epidemiologists, microbiologists, pediatricians (Expert Commission). The Commission later released a comprehensive report estimating that by 2050, over ten million deaths annually will occur due to antibiotic resistance (Expert Commission). According to Dr. Lance Price, the co-chair of the Commission, “Antibiotic resistance is one of the greatest health threats of our time” (Expert Commission). Assessing the public health impact of voluntary regulations is vital; the Centers for Disease Control and Prevention (CDC) estimates that antibiotic resistance causes over two million infections and 23,000 deaths annually in the U.S. alone. According to the Health Assembly of the World Health Organization (WHO), antibiotic resistance “poses a profound threat to human health.” This honors thesis serves as case study on the effectiveness of voluntary measures versus mandatory regulation in confronting a single aspect concerning the problem of antibiotic resistance in agriculture. The compilation of research finds that all antibiotic use must be part of a multi-faceted proactive health policy to insure proper response and mitigation of health risks. Researching economic, legislative, and health impacts of FDA

GFI #213 contribute to the discourse on fighting antibiotic resistance in the food system worldwide.

Graphic 1

Summary of Roadmap Recommendations*

A. Decreasing Livestock Use of Medically Important Antibiotics

1. Set targets for reducing antibiotic use.
2. Phase out routine or programed use of medically important antibiotics.
3. Reduce the need for antibiotics by adopting non-antibiotic best practices, and by innovating new technologies, to maintain animal health and prevent disease.
4. Eliminate antibiotic use where efficacy can no longer be demonstrated.
5. Prioritize the use in veterinary practice of antibiotics that the WHO does not categorize as "critically important" for human medicine, such that:
 - A. Antibiotics in the "Critically important" category are only used to treat animals sick with a specific bacterial disease. Use of the subset of critically important antibiotics the WHO refers to as "highest priority" also should require testing that confirms the bacterium involved is not susceptible to other antibiotics.
 - B. Do not approve for food and animal use any "critically important" antibiotics, such as carbapenems, that are not currently FDA-approved for this purpose;
6. Bolster veterinary oversight of antibiotic use with other safeguards.

B. Monitoring Antibiotic Use to Reduce Antibiotic Resistance

7. Develop a system for collecting detailed, comprehensive data on actual antibiotic use, and collect essential data.
8. Coordinate with and learn from the other countries in developing a comprehensive data collection system.
9. Adopt a metric for reporting data on antibiotic sales or use that better allows trends to be identified, explained and compared.

C. Enhancing Surveillance and Data Integration to Inform Antibiotic Use Policy

10. Integrate available data into a single, comprehensive report.
11. Improve surveillance to detect new and emerging resistance threats.
 - A. Expand surveillance for emerging resistance using next generation sequencing technology.
 - B. Expand surveillance for important emerging pathogens.
 - C. Pilot test approaches that comprehensively detect resistance in all bacteria in a sample.
 - D. Expand surveillance at the state level.

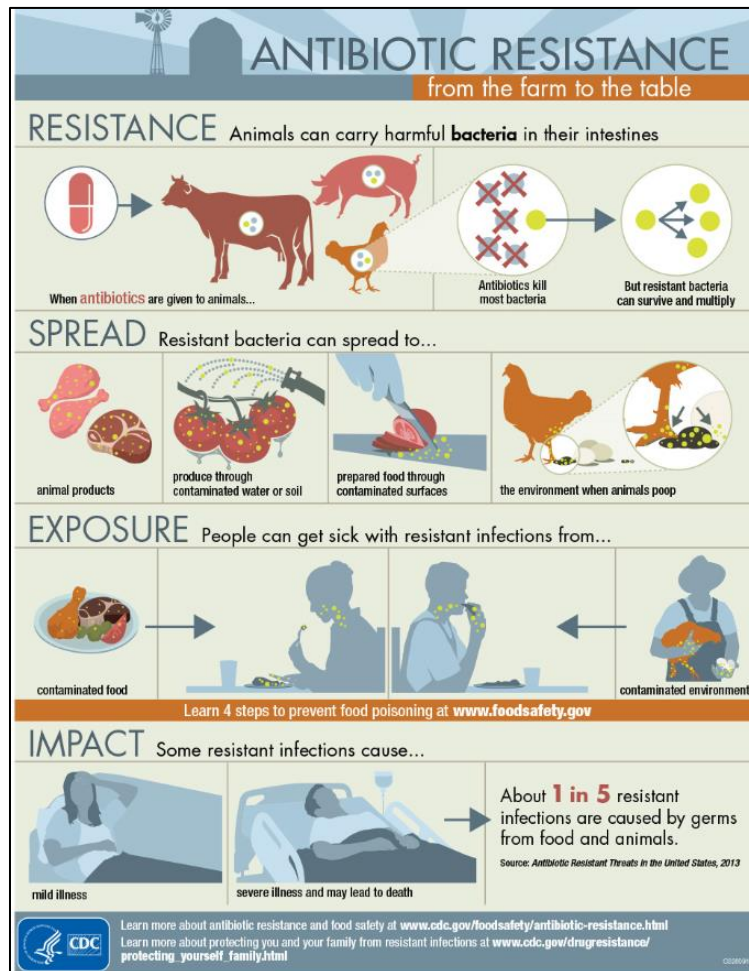
* Note: The numbering of the recommendations is not meant to connote any particular prioritization.

Source: Expert Commission on Addressing the Contribution of Livestock to the Antibiotic Resistance Crisis, *Summary of Roadmap Recommendations*, 2017; pg. 2.

Introduction: Background and Global Relevance of Topic

The discovery of antibiotics in the early 1930s revolutionized the science of medicine—disease mortality rates plummeted by 75% in the first 15 years of use (Orrico). The effectiveness of antibiotics during this time was considered miraculous, with the ability to treat previously grim diagnoses like meningitis with relative ease. It was not until the 1950s that researchers discovered a breakthrough in agricultural antibiotic use: low doses of antibiotics given to livestock regularly could prevent disease and promote growth, thus food animals reached slaughter weight faster (Orrico). Thus, in 1951, the FDA sanctioned antibiotics for use in growth production without veterinary prescription (Laxminarayan). At first, studies conducted before the 1980s indicated that antibiotic growth promoters quickened the livestock growth rate by as much as 5-15% (Laxminarayan). However, by the 2000s, this rate was less than 1%, and labelled as not significant (Laxminarayan). Nonetheless, non-therapeutic use is widely used in the modern concentrated animal feeding operations (CAFOs) that dominate the global livestock industry. As the name implies, CAFOs raise a large population of food-producing animals in a small area of space to maximize profits. Sadly, 99% of food-producing animals never step foot outside production facilities (Boris). The subsequent close quarters facilitate outbreaks of disease among the animals. To combat this, CAFOs mix low doses of antibiotics into the feed and water of the livestock in order to prevent illness and expedite weight gain. This non-therapeutic use of antibiotics has contributed to the rise in antibiotic resistant pathogens, some of which are immune to even the strongest antibiotics known to science (Orrico). Global examples, such as Denmark, illustrate how any negative impact of banning non-therapeutic antibiotic use can be counteracted through improvements in hygiene, feed, and production practices (Laxminarayan).

Graphic 2



Source: Centers for Disease Control and Prevention, *Antibiotic Resistance from the Farm to the Table*, Dec. 2017.

As pictured in graphic 2, these “super-bacteria” are passed to humans via the food or water supply, environmental waste contamination, and direct transmission from contact with infected animals (CDC). Public health researchers in China, Denmark, and the United States compiled data that indicated a rise in antibiotic-resistant environmental contamination from livestock waste, which warned agricultural antimicrobial resistance (AMR) as a crisis without national borders. As this research will demonstrate, the United States employs a select few Danish tactics to address agricultural AMR, yet displays many of the weaknesses of the Chinese approach.

Industrial farming practices have been adopted for use worldwide, including in Asia, parts of Europe, and South America. As the average income has steadily risen, so has the demand for meat, poultry, and animal products. As an example, China yields and consumes more than 500 million head of swine, more than half of the world total, and is the world's top meat producer (Collignon). Currently, there are no official bans on using antibiotics for production purposes, and antibiotics can be used with food-producing animals without any form of veterinary oversight (Maron). Ying et. al estimates that over half of antibiotics sold in China are supplied to food-producing animals (Ying et al). High levels of antibiotic resistant bacteria have been detected in animal fecal waste that contaminates nearby waterways (Collignon). The Chinese Ministry of Agriculture addressed agricultural antibiotic overuse as far back as 1987, but due to poor enforcement, little progress has been made; there is still a pervasive lack of surveillance and regulation (Ying et al). This suggests an economic bias over public health concerns.

In Denmark, however, efforts to reduce agricultural antibiotic use have facilitated success as well as domestic and international support. By 1999, medical researchers, farmers, public health officials, and Danish legislators, eliminated non-therapeutic antibiotic use in swine production. From 1994 through 2016, antibiotic use in all animals fell by 49%, while production of food animals actually increased by 15% ("DANMAP 2016"). This led to a decline in antibiotic-resistant bacteria in swine and human fecal matter—demonstrating the effectiveness of reducing agricultural antibiotic use in regards to both human and animal health (Levy). The integrated industry and policy approach in Denmark balances economic and public health interests.

Denmark Examination

European countries such as Denmark garnered striking success in banning agricultural antibiotic use for production purposes. As early as the 1960s, the EU prohibited medically important antibiotic use in agriculture for growth-promoting purposes, but the scope of the regulation was limited to a small number of drug classes (Levy). According to Hammerum et al, “Denmark was the first country to establish a systematic and continuous monitoring program of antimicrobial drug consumption and antimicrobial agent resistance in animals, food, and humans” (Hammerum et al). This comprehensive surveillance system is known as the Danish Integrated Antimicrobial Resistance Monitoring and Research Program (DANMAP), and continues to collect vital data used in epidemiological and public health research today. Before tackling the complexity of banning nontherapeutic antibiotic use in food-producing animals, public health researchers established a strong foundation of evidence based in science—rates of antibiotic resistance found in farmers and livestock treated with antibiotics (Levy). In 1994 and 1995, researchers in Denmark discovered a link between non-therapeutic use of avoparcin in food-producing animals and high levels of vancomycin-resistant *Enterococcus faecium* (VREF) on farming operations. Since avoparcin is one of only a select number of drugs able to treat resistant VREF, in spring of 1995, the Danish Minister of Agriculture and Fisheries completely outlawed agricultural use of avoparcin (Hammerum et al). This triumph in public health was possible because of the effective non-political scientific evidence collected, thus demonstrating how public health and governmental spheres can cooperate. Later after this pronouncement, EU administrators followed the Danish lead and adopted the avoparcin ban (Hammerum et al). However, Denmark incorporated a holistic approach to reducing antibiotic overuse by addressing industry pressures—namely that veterinarians received incentives for prescribing antibiotics.

According to Levy, at one point, veterinarians received a third of their salary from prescription quota incentives (Levy). To remedy this, the Danish government enacted regulations restricting profits that veterinarians could receive from drug sales. Throughout the late 1990s, Denmark continued to monitor environmental antibiotic resistance and by 1999, eradicated all non-therapeutic antibiotic use in swine operations (Levy).

The US Approach: Description of FDA GFI #213

Regulating agricultural antibiotic use in the United States has a complex history. In 1978, the FDA harbored significant concerns about antibiotic resistance arising from production uses (Eskridge). The FDA proposed three strategies: banning all Penicillin use, only using tetracyclines for treating disease, and controlling dispensing through registered feed mills by order of a veterinarian (Eskridge). This was met with uproar in Congress, with fifteen senators citing increased production costs for farmers and a lack of concrete scientific evidence proving that production uses of antibiotics cause antibiotic resistance in humans. Since then, the FDA has been reluctant to take a hard stance with mandatory regulation of antibiotic use, which has resulted in the United States using 13% of the world's total antibiotics in agriculture, second only to China (Expert Commission). The situation has not improved since then, with antibiotic resistance continuing to proliferate.

Today, despite the presence of a goldmine of international research, there is still the pervasive and willful disbelief in the connection between agricultural antibiotic resistance and human infection throughout the agricultural industry in the United States. This is due to a fundamental difference in public health principle comprehension between the U.S. and the E.U. The E.U. operates under a more literal understanding of the “precautionary principle”, being proactive “when evidence points toward the potential of an activity to cause significant

widespread or irreparable harm to public health or the environment, options for avoiding that harm should be examined and pursued even if the harm is not yet fully understood or proven” (Marshall and Levy). Part of the reason for the U.S. reluctance is due to the fact that there has not been a definitive study like the Danish ban of avoparcin use in livestock resulting in heightened VREF bacteria levels in humans. This is a glaring absence in epidemiological and environmental health research in the United States that demonstrates genetic zoonotic potential. Thus, scientific studies back-tracing resistance genes found in humans to their agricultural source is a pressing need (Schmidt). These studies have only recently begun (Schmidt). However, there are cases of infection by consumption and exposure to sick animals. For example, in 1985, there was an outbreak of drug-resistant *Salmonella* in California that sickened 1000 people, and was later attributed to meat from dairy cows (Khachatourians). Multiple studies indicate transmission through animal products to humans, finding that both the product and the human fecal matter contain the same resistant bacteria (Marshall and Levy). Additionally, researchers discovered that the DNA of resistance genes in both humans and animals is completely identical (Schmidt). Furthermore, in 2000, the National Antimicrobial Resistance Monitoring System (NARMS) concluded that based on human *Salmonella* samples, 12% was impervious to five of the major drugs also used in agriculture (Schmidt). This gives credence to the likelihood of resistance transmission between humans and food-producing animals. Though these studies provide support as evidence of the possibility of agricultural use in the U.S. directly causing resistance proliferation in humans, a large-population study truly demonstrating this connection is still in progress.

Recently Smith and Heitman conducted research exploring the connection between specific strains of human and livestock associated MRSA. Smith and Heitman acknowledged the

difference in data results between Europe and the United States. Specifically, the CC398 strain found in humans in Europe was traced back entirely to livestock sources (Smith and Heitman). However, in the United States, CC398 was found in both agricultural and non-agricultural locations. When livestock have human MRSA strains, and humans have livestock-associated MRSA strains, researchers have difficulty determining the true genetic source. The study concluded that people that lived near CAFOs had a significantly higher risk of MRSA infection, though the MRSA bacteria was not livestock-associated (Smith and Heitman). According to Smith and Heitman, this would suggest that either new strains of MRSA are evolving on farms, or that antibiotic-resistant genes are being transferred to humans and proliferating. Ultimately, Smith advocated for national, large-scale sampling on agricultural operations to give detail to this complex phenomenon.

According to the CDC, 70% of antimicrobials in the U.S. are used in livestock production (Expert Commission). Public concern and congressional pressure fueled an FDA regulatory response in the form of FDA GFI #209, and most recently, FDA GFI #213 in 2013. FDA GFI #209 outlines principles of judicious use of antimicrobials in agriculture, while GFI #213 provides the voluntary measures for producers to take in order to achieve two major goals: “Limit medically important antimicrobial drugs to uses in animals that are considered necessary for assuring animal health, and limit medically important antimicrobial drugs to uses in animals that include veterinary oversight or consultation” (FDA GFI #209, FDA GFI #213).

As a part of the strategy to regulate agricultural antibiotic distribution, the FDA categorizes dispensation methods into three categories: Veterinarian Feed Directive (VFD), prescription (RX), or over-the counter (OTC). OTC products are available to purchase and use without veterinary oversight or written permission and can be found in most feed stores. VFD

and prescriptions both require veterinary supervision and a written order required to buy the drug. VFD is mandatory for any feed-based antimicrobial product, while a prescription is required for all other routes of administration. The FDA intended to enact veterinarian oversight to antimicrobials administered to food-producing animals by route of feed or water (FDA GFI #213). As many of these antimicrobials have OTC dispensing status, the FDA created a series of voluntary guidances to shift labelling to prescription or VFD status. However, the non-mandatory nature of FDA GFI #213 has come under fire due to lack of drug use surveillance, regulatory ambiguity, indefinite goals, lenient enforcement, and poor results.

Limitations of FDA GFI #213

Guidance for Industry #213 is limited in its abilities to reduce antibiotic resistance because of its voluntary nature and focus on economic impacts rather than public health implications. The FDA has been aware of the possible health threat of antibiotic resistance arising from nontherapeutic agricultural antibiotic use since before 1977. At that time, the FDA rejected calls to place restrictions on non-therapeutic use, citing concerns about profit consequences from increased production costs for producers, suggesting a bias towards industry (Orrico). Additionally, the details of executing GFI #213 are negotiated privately between the FDA and pharmaceutical companies. Heinzerling believes that this will keep the public unaware about the progress of the voluntary measures for years to come (Heinzerling). GFI #213 states that the “FDA believes it is critically important that changes such as these be implemented to minimize impacts on veterinarians, the animal feed industry, and animal producers” (FDA GFI #213). While this serves to make the transition to prescription labelling and veterinary oversight more palatable for these parties, the time-sensitive nature of limiting the progress of antibiotic resistance is not emphasized enough. Therefore, preemptive and efficient action is necessary to

hinder the development of even stronger antibiotic resistant pathogens. Further instances in the directive's language indicate possible enforcement weaknesses.

In contrast, there are studies that support the use of antibiotics in agriculture because of the benefit to animal welfare and securing the human food supply. Animal Health Institute spokesperson Ron Phillips defended the use of non-therapeutic antibiotic use, "And to date, no one has found an alternative that can match antibiotics for disease control on the scale at which we produce food today—at least not one which allows consumers to buy meat at such low prices" (Schmidt). This statement aligns with Hao's stance that antibiotics help manage the growing demand for food. For example, antibiotics given to swine results in increased conception and milk production, lower piglet mortality rate, and faster weight gain, thus increasing the population (Hao). Furthermore, antibiotic use also prevents the spread of zoonotic pathogens to humans through the food supply (Hao). Hao stated that antibiotics, "could significantly decrease the bacterial contamination in animal products" (Hao). Antibiotic feed additives result in decreased bacterial contamination within animal carcasses, thus limiting the infection risk to humans (Hao). Hao concluded that even though the studies demonstrating the benefits of antibiotic use were limited in scale and explanation, "It is undeniable that rational use of antimicrobials plays a vital role in the production of food animals and protecting public health" (Hao). Therefore, agricultural antibiotic use protecting food security is a public health counter-claim.

However, there are significant concerns with Hao's argument. For example, even though animal carcasses may have decreased bacteria, this does not pay homage to the fact that the products from these animals includes low-doses of antibiotics (Boris). It is possible that these food-producing animals carry resistant bacteria without showing any clinical symptoms, and pass

the meat inspection process (Boris). Hao also ignored the problem of environmental contamination as a public health concern. According to the USDA, livestock create 500 million tons of manure per year (Boris). Coupled with the fact that up to 75% of antibiotics fed to livestock are present in their manure, this proves to be a serious issue, not to be pushed aside in favor of cheap meat (Boris). In fact, a consumer survey conducted by the Review on Antimicrobial Resistance concluded that 86% of consumers would like antibiotic-free animal products, and 60% of those surveyed were willing to pay more for it ("Review"). Healthcare costs to the consumer from an antibiotic resistant infection are far higher than the comparably negligible price increase in animal products that would be a result of banning non-therapeutic drug use. For example, it is estimated that human disease resulting from non-therapeutic agricultural drug use piles on more than \$50 billion to the cost of healthcare in the United States (Boris). In addition, the cost advantage in production possible through non-therapeutic antibiotic use may be trifling compared to the substantial export losses, according to Landers et al.

Landers et al addressed the possible large-scale economic consequences of not increasing agricultural antibiotic control. In the study, researchers collected agricultural antibiotic regulation data from seventeen different countries that are trade partners with the United States. The conclusion was that the majority among these trade partners have stricter limits on antibiotic use, including mandatory veterinary oversight. According to Landers et al, because the FDA continues to support use of antibiotics for disease prevention, this could prove to be a disadvantage for U.S. exports of food animal products. For example, Landers et al found that since 1997 when the European Union banned U.S. poultry imports because of antimicrobial rinse residue, U.S. imports went from 52 million dollars to 13 million dollars as of 2011 (Landers et al). Most trade partners that import American animal products have stricter policies, such as

Sweden, Denmark, and the Netherlands (Maron). Therefore, antibiotic policy trade barriers abroad account for a loss of export revenue that may rival an increase in production costs due to more stringent antibiotic regulation. The environmental pollution and skyrocketing health costs because of agricultural AMR perhaps eclipses the food availability counter-argument.

GFI #213 was written as a voluntary guideline in order to ensure efficiency in the overhaul process (Rosso Grossman). According to the FDA, the document, “do[es] not establish legally enforceable responsibilities” (FDA GFI #213). Instead, guidances describe the FDA’s current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word ‘should’ in the FDA’s guidances means that something is suggested or recommended, but not required” (FDA GFI #213). This disclaimer denies legislative power, and instead operates through the soft power of suggestion. However, guidances lack enforcement methods or legal consequences for infractions. FDA GFI #213 is linked to multiple regulatory documents, such as FDA GFI #209 and the Veterinary Feed Directive (VFD), in a concentrated effort to convince producers and pharmaceutical companies to regulate antibiotic usage through changing label wording. Before 1993, antibiotics were available over the counter for animal feeding operations as feed and water additives. If pharmaceuticals edit labels to state the necessity of veterinary supervision, only approved usage would be possible, since it is currently against the law to use an antibiotic for extra-label purposes. Although this helps in tracking antibiotic use and controlling the conditions in which antibiotics are prescribed, there are a number of issues, such as oversight consistency and geographical limitations. A key facet of the document is veterinary management in prescribing antibiotics. The veterinarian carries responsibility for deciding if/when/how an antibiotic is able to be judiciously used. Since this can be subjective, training, education, and

further veterinarian presence would be necessary to prescribe based upon a common definition of judicious use. Unlike in Denmark, there is no limit to veterinarian profits, and no subsequent data on prescription rates per each veterinarian (Expert Commission). This is an issue due to the lack of accountability for veterinarians to use antibiotics in a prudent manner. Rural and small-scale farming operations may not have access to regular veterinary care, limiting the geographic scope of FDA GFI #213's area of effectiveness. According to Heinzerling, the release of the VFD undermines the veterinary oversight conditions present in FDA GFI #213. VFD essentially reduces the frequency of veterinary documentation, working against previous requirements (Heinzerling; Rosso Grossman). This represents a fundamental conflict within the FDA GFI #213 in regards to combatting agricultural antibiotic resistance.

New antibiotics are the primary focus of FDA GFI #213. This is relevant because it suggests the FDA is trying to address agricultural antibiotic resistance proactively, which is an effective tactic, but may draw attention away from older antibiotics still in use. For example, as of 2003, the FDA requires safety reviews for every new veterinary antibiotic as a pre-approval process. Despite this, the majority of antibiotics given to food animals as growth enhancers, disease prevention, and other non-therapeutic applications are exempt, because the FDA approved them before 2003 (IDSA). According to Heinzerling, voluntary measures, "guarantee little more than continued delay in tackling a public health risk" (Heinzerling). Heinzerling further explains that there are key weaknesses in FDA GFI #213. The FDA still endorses sub-therapeutic use of antibiotics to prevent disease; this means that antibiotics could still be used on a mass scale, even without active infection present. Furthermore, the success of FDA GFI #213 relies upon the cooperation of pharmaceutical companies, which are driven by profit. Twenty-five out of twenty-six pharmaceutical companies contacted by the FDA have accepted the

voluntary initiative to re-label drugs from over the counter to prescription or veterinary oversight. While this is positive on the surface, these companies have not agreed to do this for every drug, and there are currently legal disagreements over which drugs are considered medically important. Heinzerling suggests that even though production uses of antibiotics may be phased out, companies will merely use the aforementioned loophole and label the drugs under disease prevention. The suggestions of FDA GFI #213 have an implementation phase of three years, however, the FDA has not outlined a clear back-up plan in case of failure (Heinzerling).

According to FDA GFI #213, “If, after the period of evaluation of the three-year phase in, [the FDA] determine[s] that adequate progress has not been made, [the FDA] will consider whether further action under the existing provisions of the FD&C Act may be appropriate” (“FDA GFI #213”). This deliberately vague statement appears to be a veiled threat for mandatory regulation in the wake of non-compliance. However, the lack of specificity regarding clauses of the FD&C Act and their consequences undermines the authority of the statement. Furthermore, even the three-year adoption period is not concrete. Again, the FDA contradicts their authority by hedging, “Although FDA is committed to completing this rulemaking process within the 3-year timeframe for implementing the changes discussed in this guidance, FDA is prepared to extend the timeframe, as necessary, to ensure that it coincides with the implementation of the revised VFD requirements” (“FDA GFI #213”). This essentially writes a blank check to pharmaceutical companies for adopting the necessary changes, and renders the threat of mandatory legal action a mere bluff. Thus, these gaps in regulation allow for the continued antibiotic misuse that contribute to antibiotic resistance.

How Effective is FDA GFI #213?

Since the inception of FDA GFI #213 back in 2013, the ultimate goal was to gradually implement measures to re-label medically important antibiotics from OTC to VFD or prescription, with all claims for production uses removed. To monitor the progress of GFI #213, the FDA releases an annual report that contains data estimates for antimicrobial drugs approved for use in food-producing animals. This document includes the drug class, medical importance status, and dispensation method. Recently, in December 2017, the FDA released the “FDA 2016 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals” to the public.

There was recent positive progress regarding the implementation of FDA GFI #213 between 2015 and 2016. According to the FDA’s 2016 Summary Report, the overall sales and distribution of approved antimicrobials for food-producing livestock in the United States fell by 10%. In comparison, from 2014 to 2015, the overall total increased by 1%. This decrease is indeed a welcome change. In 2015, 62% of all antimicrobials sold domestically were categorized as medically important to human health. This percentage fell by a mere 2% in 2016 to 60% (“2016 Summary Report”). Nevertheless, the majority of antimicrobials used on food-producing animals continue to be medically important. Reducing the consumption of these vital groups of antimicrobials is essential to preserving the efficacy of antibiotic treatments in humans.

United States 2016 Production Totals and Medically-Important Antibiotic Sales

Food-Producing Animal	Production (millions)	Antibiotics Distributed (kg)
Cattle	92.0	3,610,943
Swine	67.6	3,133,262

Source: United States Food and Drug Administration, *2016 Summary Report On Antimicrobials Sold or Distributed for Use in Food-Producing Animals*, Dec. 2017.

Even though the 2016 report indicated a 10% decrease in antibiotic sales from 2015 to 2016, one of the key issues hindering the fight to reduce antibiotic use is the lack of thoroughness in FDA data collection. The table above is an example of how the FDA now records livestock population with aggregate antibiotic totals. The 2016 report displays this latest addition to antibiotic surveillance—estimated amounts of antibiotics administered categorized by species. However, this update has been far too long removed. Alarming, the FDA only began collecting antibiotic use data by species in 2016.

U.S. 2009-2016 Swine Production Totals and Medically-Important Antibiotic Sales

Year	2009	2010	2011	2012	2013	2014	2015	2016
Production (millions)	65.4	64.0	64.0	64.9	65.9	62.9	65.9	67.6
Antibiotics Distributed (kg)	--	--	--	--	--	--	--	3,133,262

Source: USDA, *Quarterly Hogs and Pigs*, 2009-2016; FDA, *2016 Summary Report On Antimicrobials Sold or Distributed for Use in Food-Producing Animals*, Dec. 2017.

This means that for the duration of the adaptation period of FDA GFI #213, the FDA did not collect specific records of antibiotic use broken down by species. The table above contains the total production of swine in the United States, along with the estimated amount of antibiotics used. The USDA records the population totals of both cattle and swine, while the FDA provides the antibiotic estimates. The blank spaces in the table section for antibiotic distribution serves as a visual representation of the vitality of complete data collection. However, even without species-specific data, the argument for non-therapeutic use weakens. According to the table above, the swine population from 2009 through 2016 has been relatively stable. This indicates that though until 2015 antimicrobial use continued to rise, production has not followed suit. Determining areas of overuse and taking steps to address the situation is possible only with detailed data. This is a tactic long used by DANMAP in Denmark and provides a baseline for the amounts of drugs target groups of livestock are consuming.

Table 1

ANTIMICROBIAL DRUGS APPROVED FOR USE IN FOOD-PRODUCING ANIMALS ¹ ACTIVELY MARKETING IN 2016 DOMESTIC SALES AND DISTRIBUTION DATA REPORTED BY MEDICAL IMPORTANCE AND DISPENSING STATUS				
	Dispensing Status	Annual Totals (kg) ²	% Subtotal	% Grand Total
Medically Important³	<i>OTC^{4,5,10}</i>	8,005,726	96%	57%
	<i>RX^{4,6}</i>	237,366	3%	2%
	<i>RX⁶/OTC^{4,5,7}</i>	60,705	1%	<1%
	<i>VFD⁸</i>	57,943	1%	<1%
	Subtotal	8,361,740	100%	60%
Not Medically Important⁴	<i>All Dispensing Statuses⁹</i>	5,621,276		40%
	Grand Total	13,983,016		100%

¹ Includes antimicrobial drug applications which are approved and labeled for use in both food-producing animals (e.g., cattle and swine) and nonfood-producing animals (e.g., dogs and horses).

² kg = kilogram of active ingredient. Antimicrobials which were reported in International Units (IU) (e.g., Penicillins) were converted to kg. Antimicrobial class includes drugs of different molecular weights, with some drugs reported in different salt forms.

³ Guidance for Industry #213 states that all antimicrobial drugs and their associated classes listed in Appendix A of FDA's Guidance for Industry #152 are considered "medically important" in human medical therapy.

⁴ Not Medically Important refers to any antimicrobial class not listed in Appendix A of FDA's Guidance for Industry #152.

⁵ OTC = Over-The-Counter. Approved animal drugs that are available without a prescription or veterinary feed directive.

⁶ Rx = Prescription. Approved animal drugs that require a prescription from a licensed veterinarian.

⁷ Animal drugs that were approved with both a prescription and OTC dispensing status (RX/OTC), with the approved drug being marketed with either a prescription label or an OTC label, depending upon the species and indication on the label.

⁸ VFD = Veterinary Feed Directive. Approved animal drugs that are intended for use in or on animal feed and must be used under the professional supervision of a licensed veterinarian.

⁹ The All Dispensing Statuses category includes the following: OTC, RX/OTC, and VFD.

¹⁰ As part of the implementation of Guidance for Industry (GFI) #213, the dispensing status of some of the medically important antimicrobial products affected by GFI #213 started to change from OTC to either Rx or VFD during 2016. Sales and distribution data for each product are reported to FDA broken out for each month of the calendar year; thus, the sales data in this summary report reflect the dispensing status of each product as reported to FDA for any particular month. The implementation of GFI #213 was completed in January 2017; all remaining affected products transitioned from OTC to either Rx or VFD marketing status at that time. The 2017 Summary Report will reflect the full transition of all medically important antimicrobials affected by GFI #213 from OTC to either Rx or VFD.

Source: United States Food and Drug Administration, *2016 Summary Report On Antimicrobials Sold or Distributed for Use in Food-Producing Animals*, Dec. 2017; table 6.

In Table 1, taken from the FDA Annual Report for 2016, the totals of medically important antimicrobial drugs are given based on dispensing status. Prescription and VFD dispensing make up less than 5% of annual antimicrobial consumption. This is problematic, as OTC drug use continues to be unregulated. Observing trends from 2015 to 2016 in Table 2, the

dispensing category of antimicrobials continued to dominate as OTC, from 97% to 96%, despite the relabeling efforts of FDA GFI #213 (“2015 Summary Report”).

Table 2

ANTIMICROBIAL DRUGS APPROVED FOR USE IN FOOD-PRODUCING ANIMALS ¹ ACTIVELY MARKETED 2009-2016 PERCENTAGE OF DOMESTIC SALES AND DISTRIBUTION <u>MEDICALLY IMPORTANT² ONLY</u> <u>REPORTED BY DISPENSING STATUS</u>								
Dispensing Status	2009 % Sales and Distribution	2010 % Sales and Distribution	2011 % Sales and Distribution	2012 % Sales and Distribution	2013 % Sales and Distribution	2014 % Sales and Distribution	2015 % Sales and Distribution	2016 % Sales and Distribution
OTC ^{3,8}	98%	98%	97%	97%	98%	97%	97%	96%
Rx ⁴ /OTC ^{3,5}	0.57%	0.58%	0.61%	0.62%	0.60%	0.51%	0.58%	0.73%
Rx ⁴ or VFD ^{6,7}	2%	2%	2%	2%	2%	2%	2%	4%
Subtotal	100%	100%	100%	100%	100%	100%	100%	100%

¹ Includes antimicrobial drug applications which are approved and labeled for use in both food-producing animals (e.g., cattle and swine) and nonfood-producing animals (e.g., dogs and horses).

² Guidance for Industry #213 states that all antimicrobial drugs and their associated classes listed in Appendix A of FDA’s Guidance for Industry #152 are considered “medically important” in human medical therapy.

³ OTC = Over-The-Counter. Approved animal drugs that are available without a prescription or veterinary feed directive.

⁴ Rx = Prescription. Approved animal drugs that require a prescription from a licensed veterinarian.

⁵ Animal drugs that were approved with both a prescription and OTC dispensing status (Rx/OTC), with the approved drug being marketed with either a prescription label or an OTC label, depending upon the species and indication on the label.

⁶ VFD = Veterinary Feed Directive. Approved animal drugs that are intended for use in or on animal feed and must be used under the professional supervision of a licensed veterinarian.

⁷ The “Rx or VFD” category includes four VFD products marketed by only two distinct sponsors; therefore, VFD products cannot be independently reported (excluding 2013 through 2016).

⁸ As part of the implementation of Guidance for Industry (GFI) #213, the dispensing status of some of the medically important antimicrobial products affected by GFI #213 started to change from OTC to either Rx or VFD during 2016. Sales and distribution data for each product are reported to FDA broken out for each month of the calendar year; thus, the sales data in this summary report reflect the dispensing status of each product as reported to FDA for any particular month. The implementation of GFI #213 was completed in January 2017; all remaining affected products transitioned from OTC to either Rx or VFD marketing status at that time. The 2017 Summary Report will reflect the full transition of all medically important antimicrobials affected by GFI #213 from OTC to either Rx or VFD.

Source: United States Food and Drug Administration, *2016 Summary Report On Antimicrobials Sold or Distributed for Use in Food-Producing Animals*, Dec. 2017; table 13b.

The examination of antibiotic distribution data over a broader period of time overshadows the progress of FDA GFI #213 touted in the 2016 report; the success outlook is bleak. As said before, the annual reports released by the FDA began in 2009. The data trends

between 2009 through 2016 reflect the general status and effectiveness of FDA GFI #213 in the present. Over this span of years, the domestic sale and distribution of antimicrobials actually rose 11% by the end of 2016 (“2016 Summary Report”).

While the 2009 through 2016 total reflects both before and after the introduction of FDA GFI #213, it is vital to include both time periods in order to understand the true impact of FDA GFI #213. To further strengthen this point, even looking at the data from 2013 through 2016, there was a marked increase until 2016, when the total antimicrobial sales began to slightly decrease.

Table 3

ANTIMICROBIAL DRUGS APPROVED FOR USE IN FOOD-PRODUCING ANIMALS ¹ ACTIVELY MARKETED 2009-2016 PERCENTAGE OF DOMESTIC SALES AND DISTRIBUTION <u>MEDICALLY IMPORTANT² ONLY</u> <u>REPORTED BY INDICATIONS</u>								
Indications	2009 % Sales and Distribution	2010 % Sales and Distribution	2011 % Sales and Distribution	2012 % Sales and Distribution	2013 % Sales and Distribution	2014 % Sales and Distribution	2015 % Sales and Distribution	2016 % Sales and Distribution
<i>Production³ or Production/Therapeutic^{1,5} Indications</i>	72%	71%	70%	68%	72%	72%	71%	69%
<i>Therapeutic Indications Only^{1,4}</i>	28%	29%	30%	32%	28%	28%	29%	31%
Subtotal	100%	100%	100%	100%	100%	100%	100%	100%

¹ Includes antimicrobial drug applications which are approved and labeled for use in both food-producing animals (e.g., cattle and swine) and nonfood-producing animals (e.g., dogs and horses).

² Guidance for Industry #213 states that all antimicrobial drugs and their associated classes listed in Appendix A of FDA's Guidance for Industry #152 are considered "medically important" in human medical therapy.

³ As part of the implementation of Guidance for Industry (GFI) #213, production indications (e.g., increased rate of weight gain or improved feed efficiency) of some of the medically important antimicrobial products affected by GFI #213 started to be removed from product labeling during 2016. Sales and distribution data for each product are reported to FDA broken out for each month of the calendar year; thus, the sales data in this summary report reflect the indication(s) on the labeling of each product as reported to FDA for any particular month. The implementation of GFI #213 was completed in January 2017; all remaining affected products removed production indications from their labeling at that time. The 2017 Summary Report will reflect the full removal of production indications from the labeling of all medically important antimicrobials affected by GFI #213.

⁴ Therapeutic Indications (e.g., treatment, control, or prevention of a specific disease).

⁵ From 2009 to 2014 there were fewer than three distinct sponsors marketing antimicrobial animal drugs with only production indications (i.e., with no therapeutic indications). To protect confidential business information these data cannot be independently reported and are, therefore, combined with the data for drugs with both production and therapeutic (production/therapeutic) indications. In 2015 and 2016, there were no products that only have production claims.

Source: United States Food and Drug Administration, *2016 Summary Report On Antimicrobials Sold or Distributed for Use in Food-Producing Animals*, Dec. 2017; table 12b.

Most notably, the summative sales and distribution of antimicrobials for production and therapeutic usage has only declined from 72% in 2009 to 69% in 2016. Table 3 displays the full range of percentages from 2009 through 2016 (“2016 Summary Report”). One of the foremost objectives of FDA GFI #213 is eliminating antibiotics used for production purposes. However, there is a gap in the data collection and formatting for the FDA’s annual report. Due to privacy protection procedures for businesses, the FDA cannot provide the information regarding medically important drugs used for production reasons—in lieu of this, sole production is combined with therapeutic use. However, the FDA estimates that 10% to 15% of antibiotics are still used for growth enhancement purposes only (Expert Commission). Separating production use from therapeutic use is currently not possible with current FDA protocols. Therefore, it is problematic when determining the progress of reducing nontherapeutic antibiotic use in agriculture through the amounts and allocation of antimicrobials in these reports. This blatant subterfuge is an example of FDA industry partiality.

Table 4

ANTIMICROBIAL DRUGS APPROVED FOR USE IN FOOD-PRODUCING ANIMALS ¹ ACTIVELY MARKETING IN 2016 DOMESTIC SALES AND DISTRIBUTION DATA REPORTED BY MEDICAL IMPORTANCE AND INDICATIONS				
	Indications	Annual Totals (kg) ²	% Subtotal	% Grand Total
Medically Important³	<i>Production^{5,6}/Therapeutic⁷ Indications¹</i>	5,776,055	69%	41%
	<i>Therapeutic Indications Only^{1,7}</i>	2,585,685	31%	18%
	Subtotal	8,361,740	100%	60%
Not Medically Important⁴	<i>Production Indications Only⁵</i>	98,820	2%	1%
	<i>Production⁵/Therapeutic⁷ Indications</i>	4,202,735	75%	30%
	<i>Therapeutic Indications Only⁷</i>	1,319,721	23%	9%
	Subtotal	5,621,276	100%	40%
Grand Total		13,983,016		100%

¹ Includes antimicrobial drug applications which are approved and labeled for use in both food-producing animals (e.g., cattle and swine) and nonfood-producing animals (e.g., dogs and horses).

² kg = kilogram of active ingredient. Antimicrobials which were reported in International Units (IU) (e.g., Penicillins) were converted to kg. Antimicrobial class includes drugs of different molecular weights, with some drugs reported in different salt forms.

³ Guidance for Industry #213 states that all antimicrobial drugs and their associated classes listed in Appendix A of FDA's Guidance for Industry #152 are considered "medically important" in human medical therapy.

⁴ Not Medically Important refers to any antimicrobial class not listed in Appendix A of FDA's Guidance for Industry #152.

⁵ Production Indications (e.g., increased rate of weight gain or improved feed efficiency).

⁶ As part of the implementation of Guidance for Industry (GFI) #213, production indications of some of the medically important antimicrobial products affected by GFI #213 started to be removed from product labeling during 2016. Sales and distribution data for each product are reported to FDA broken out for each month of the calendar year; thus, the sales data in this summary report reflect the indication(s) on the labeling of each product as reported to FDA for any particular month. The implementation of GFI #213 was completed in January 2017; all remaining affected products removed production indications from their labeling at that time. The 2017 Summary Report will reflect the full removal of production indications from the labeling of all medically important antimicrobials affected by GFI #213.

⁷ Therapeutic Indications (e.g., treatment, control, or prevention of a specific disease).

Source: United States Food and Drug Administration, *2016 Summary Report On Antimicrobials Sold or Distributed for Use in Food-Producing Animals*, Dec. 2017; table 5.

According to Table 4, even in 2016, only 31% of antibiotics important to human health are used solely for therapeutic use in food-producing animals. Furthermore, only 4% of the total amount of medically-important antimicrobial drugs are dispensed as prescription or through VFD. After all of the emphasis on relabeling in order to transition OTC antimicrobials to VFD or prescription, the data reflects only a faint rise from 2% in 2009 to 4% in 2016. Based upon these

comparisons, FDA GFI #213 has not led to a significant decrease of antimicrobials used in food-producing animals. The reports in subsequent years will continue to demonstrate the efficacy or ineptitude of FDA GFI #213; in particular, January 2017 marked the deadline for the execution of these modifications. The FDA's 2017 annual report will be released in December 2018, and will contain data representing the full extent of FDA GFI #213's regulatory scope.

Though these documents embody progress in industry scrutiny and data collection, there are several vital constraints and inadequacies within the FDA's annual reports. Near the beginning of the document, there is a significant disclaimer on the reliability of the figures and information. According the FDA GFI #213, "...the sales and distribution data submitted by animal drug sponsors and summarized in this report are not indicative of how these antimicrobial drugs were actually used in animals." This connotes veterinarians condoning the extra-label use of antibiotics for a different therapeutic reason or for use with another species. Because each drug is typically able to be used for multiple reasons, it is difficult to pinpoint the exact purpose and treatment details. Another restraint to the faculty of the annual reports is the omission of any data that could be isolated to a drug or livestock producer. This is in order to protect confidential business information. However, without specific and detailed surveillance of agricultural antibiotic use in regards to geographic regions and individual operations, accountability of judicious use may be inhibited. With this, the FDA demonstrates an industry bias over public health. These are details to consider when determining the effectiveness of FDA GFI #213 when evaluating the FDA's annual agricultural antibiotic sales and distribution summary reports with Denmark's annual DANMAP releases.

Denmark's Remarkable Surveillance System

In comparison to Denmark's wide-sweeping and dynamic approach to curbing agricultural antibiotic use, FDA GFI #213 does not have neither the immediate nor long-term results. The table below contains DANMAP data dating back to the early 1990s. When researchers initially collected livestock population data, pharmaceutical companies submitted antibiotic sales and distribution as a lump sum for all food-producing animals ("DANMAP 2001"). However, after a major conference on AMR in Copenhagen in 1997, Danish legislators and public health officials initiated the VetStat programme in order to close the accuracy gap in surveillance between human and animal antimicrobial consumption. This innovative system required veterinarians and feed mills by law to submit detailed information on antimicrobial use. As a result, in 2001, DANMAP annual reports now included detailed tables with antimicrobial consumption by species and age. Interestingly enough, there were notable discrepancies between VetStat totals and totals provided by pharmaceutical companies. DANMAP concluded that this improved accuracy was vital in monitoring resistance rates and compliance with regulations. Each year, VetStat collects the production of each type of livestock, along with antibiotic use broken down by stage of life. This compilation of detailed information debunks common misconceptions plaguing antibiotic reduction efforts.

To further denote the weaknesses of the FDA's approach to curbing agricultural antibiotic use, examples from both Denmark and U.S. are provided below. The visual and informational contrast of the FDA's annual surveillance reports and Denmark's DANMAP releases is undeniable. The first table below is the 2016 general antimicrobial sales in Demark. The second one is the FDA's equivalent table for 2016. Notice the differences in data collection—age and drug type is given in DANMAP, while the FDA table only gives sums by

species. This omission creates difficulties when determining where, how, and when dosing takes place during livestock production processes.

2016 Antimicrobial Agents Sold in Denmark

ATCvet code	QJ01B	QJ01G	QJ01D	QJ01MA	QJ01FF	QJ01FA	QJ01MB	QJ01CE	QJ01CA	QJ01XQ	QJ01E	QJ01AA			
Therapeutic group	Amphenicals	Aminoglycosides	Cephalosporins	Fluoroquinolones	Lincosamides	Macrolides	Other quinolones	Penicillins, b-lactamase sensitive	Penicillin's, others(a)	Pleuromutins	Sulfonamides and trimethoprim	Tetracyclines	Other AB	Total 2015	Total 2016
Pigs	371	4163	<1	<1	1875	10113	0	15588	8286	7820	6615	22453	864	81499	78150
Sows and piglets	258	1666	<1	<1	436	528	0	8331	3512	999	4770	1698	102	23366	22300
Weaners	106	2357	<1	0	734	6665	0	1680	3961	2868	1594	13733	752	34985	34449
Finishers	7	140	<1	<1	705	2920	0	5578	813	3953	251	7022	10	23148	21401
Cattle	656	742	66	<1	3	273	0	7719	809	0	1038	1604	10	13150	12920
Intramammaries	0	31	55	0	1	0	0	257	147	0	6	0	<1	503	498
Cows and bulls excl. intramammaries	12	240	10	<1	1	114	0	6862	497	0	893	999	<1	10244	9629
Calves <12 months	635	445	1	<1	<1	155	0	467	152	0	128	567	9	2241	2561
Heifers and steers	8	26	<1	0	<1	4	0	133	13	0	10	37	<1	162	232
Poultry	5	60	0	<1	24	153	0	236	218	<1	111	748	6	2440	1560
All poultry excl. turkeys	<1	36	0	<1	18	103	0	168	97	<1	106	414	0	1931	942
Turkeys	4	24	0	0	6	50	0	67	121	0	5	334	6	509	619
Other production animal species	315	325	<1	<1	160	789	893	1	2054	0	2284	795	<1	8146	7617
Aquaculture	314	0	0	<1	0	0	893	0	11	0	1071	<1	0	2969	2289
Fur animals	2	325	0	0	160	789	0	1	2043	0	1213	794	0	5177	5327
Companion animals^(b)	1	15	137	14	69	3	0	29	717	<1	1393	45	31	2312	2458
Pets (estimated) ^(c)	<1	14	137	14	69	3	0	20	717	<1	276	40	31	1245	1326
Horses (estimated)	<1	<1	<1	<1	0	<1	0	8	<1	0	1117	5	<1	1067	1131
Other ^(d)	5	175	3	3	7	22	<1	766	245	11	283	130	1	2194	1647
Total	1353	5480	206	17	2139	11353	892	24339	12329	7832	11724	25775	913	109741	104352

Note: Data for 2015 and 2016 were extracted from VetStat 22 August 2017. Only the ATCvet group contributing mostly to the antimicrobial group is mentioned. Combination drugs are divided into active compounds

a) Penicillins with extended spectrum and combination penicillins, incl. b-lactamase inhibitors

b) In DANMAP 2016, new principles have been applied to estimate the antimicrobial use for companion animals, please see section 4.3.4

c) Approximately 222 kg of the sulfonamides and trimethoprim registered for pets are products (oral paste) typically used for horses

d) This includes data on antimicrobial agents used for sheep and goats (14 kg), data where the animal species has not been defined or where the age group does apply to the designated animal species

Source: Danish Integrated Antimicrobial Resistance Monitoring and Research Programme, *DANMAP 2016*, Oct. 2017; table 4.1.

2016 Antimicrobial Agents Sold in United States

ANTIMICROBIAL DRUGS APPROVED FOR USE IN FOOD-PRODUCING ANIMALS¹ ACTIVELY MARKETED IN 2016

DOMESTIC SALES AND DISTRIBUTION DATA REPORTED BY SPECIES-SPECIFIC ESTIMATED SALES

	Species	Estimated Annual Totals (kg) ¹	% Subtotal	% Grand Total
Medically Important³	Cattle	3,610,943	43%	26%
	Swine	3,133,262	37%	22%
	Chicken	508,800	6%	4%
	Turkey	756,620	9%	5%
	Other ²	352,114	4%	3%
	Subtotal	8,361,740	100%	60%
Not Medically Important⁴	Cattle	3,116,106	55%	22%
	Swine	425,568	8%	3%
	Chicken	1,700,124	30%	12%
	Turkey	379,478	7%	3%
	Subtotal	5,621,276	100%	40%
	Grand Total	13,983,016		100%

¹ kg = kilogram of active ingredient. Antimicrobials were reported in number of units sold or distributed and were converted to kg. Antimicrobial class includes drugs of different molecular weights, with some drugs reported in different salt forms.

² The Other category includes estimates of product sales intended for use in (1) species listed on the approved label other than cattle, swine, chickens, and turkeys, including nonfood-producing animal species (e.g., dogs and horses) and minor food-producing species (e.g., fish); (2) other species not listed on the approved label; and (3) unknown uses.

³ Guidance for Industry #213 states that all antimicrobial drugs and their associated classes listed in Appendix A of FDA's Guidance for Industry #152 are considered "medically important" in human medical therapy.

⁴ Not Medically Important refers to any antimicrobial class not listed in Appendix A of FDA's Guidance for Industry #152.

Source: United States Food and Drug Administration, *2016 Summary Report On Antimicrobials Sold or Distributed for Use in Food-Producing Animals*, Dec. 2017; table 2b.

Is This Enough to Expect from the U.S. Program?

One of the central arguments contradicting antibiotic reduction was the rise of production cost due to higher rates of livestock mortality. However, Danish farmers transformed animal husbandry procedures, and the results have been astounding. The agricultural system in Denmark has a different structure when compared to the United States. Though there are many large livestock operations, most are privately owned. Farmer cooperatives manage all aspects of production, such as slaughter and dairy plants. In turn, this fosters a sense of accountability and pride within the farming community (Levy). For example, instead of separating sows from piglets immediately and supplementing the piglets' with low-dose antibiotics, sows and piglets remain together for a longer period of time, so that the piglets can build a strong immune system from their mothers' milk. This reduced the later need for antibiotics.

Samples collected from swine since the avoparcin ban in 1995 indicate decreased rates of VREF (Levy). According to data collected by Van den Bogaard AE, et al in the Netherlands, VREF amounts decreased in both swine and humans (Van den Bogaard AE, et al). In regards to increased cost and mortality, after an initial mortality increase in swine in the years directly proceeding the 1995 and 1999 edicts, populations flourished. In 1992, the total of weaning pigs was only 18.4 million. By 2008, production had increased to 27.1 million (Levy). The production cost of each pig from birth to slaughter has increased by a single euro, equating to about 1% (Levy). The table below lists swine production alongside antibiotic use by year, sourced from the annual DANMAP reports. According to the table, swine production has continually increased, with antibiotic levels eventually levelling off in 2009 before sharply falling. Even after Levy's discoveries, production continues to expand. With improved production methods and less disease, the livestock industry in Denmark profited from the ban on non-therapeutic antibiotic

use (Levy; Rogers). Viewing Denmark as a case study, through multidisciplinary action involving health researchers, government legislators, farmers, and veterinarians, progress mutually beneficial to human and animal health and economic interests is within reach.

Danish Swine Production and Antibiotics Sold 1990-2016

Year	Production (millions)	Antibiotics Used (million kg)
1990	16.425	--
1992	18.442	--
1994	20.651	--
1996	20.424	--
1998	22.738	--
2000	22.414	--
2001	23.199	69,418
2002	24.203	72,833
2003	24.434	80,948
2004	25.141	92, 690
2005	25.758	92,532
2006	25.763	91,405
2007	26.311	97,751
2008	27.078	97,013
2009	27.603	103,697
2010	28.505	100,527

2011	29.399	81,443
2012	29.047	85,870
2013	28.996	90,606
2014	29.926	86,020
2015	30.874	81,499
2016	31.660	78,150

Source: Danish Integrated Antimicrobial Resistance Monitoring and Research Programme, *DANMAP*. 2001-2016.

Denmark's multi-dimensional plan of action includes strict mandatory components, which contrasts with the voluntary nature of FDA GFI #213. For example, the table above indicates a rise in antibiotic use on Danish swine operations from the early 2000s through 2009. The production is listed in the millions of heads, while the total antibiotics used is a sum of antibiotics used at each denoted age. Though the antibiotics were used for therapeutic purposes, this unrelenting rise was worrying. Legislators enacted the Yellow Card Initiative using the detailed data VetStat and DANMAP collected. This regulation set concrete limits of antibiotics for swine producers, which veterinarian authorities enforced with compulsory antibiotic reductions and fines ("DANMAP 2016"). Enforcement was possible because of the Danish Central Husbandry Register (CHR), which assigns each farm a number, and collects business and geographic data such as ownership, farm size, livestock type and number ("DANMAP 2016").

What the United States can learn from Denmark

American legislators, public health officials, and members of the agricultural industry can modify the strategies that Danish legislators and researchers employed to improve the antibiotic resistance outlook. First of all, comprehensive, detailed, and accurate surveillance of agricultural antibiotic use is crucial. The FDA does not have the surveillance capabilities necessary to impose parameters of antibiotic use because of the OTC status of many antimicrobials, along with a dearth of geographically targeted pharmaceutical records due to legal protections for industry. This is evident in the multiple gaps and loopholes within FDA GFI #213. An exemplary system to emulate would be VetStat in Denmark, which collects data daily from pharmacies in order to accurately track antibiotic use in food-producing animals (“DANMAP 2016”). The Expert Commission on Addressing the Contribution of Livestock to the Antibiotic Resistance Crisis recommended that the CDC, FDA, and USDA, “should publish a joint, integrated report that summarizes the following: antibiotic resistance data, antibiotic sales, antibiotic use data, and livestock production statistics” in order to modernize and streamline the scattered antibiotic resistance surveillance programs (Expert Commission). Knowing where, how, why, and what drugs are dispensed to food producing animals is essential in providing a strong scientific basis to not only target overuse, but to create a convincing report to impress upon government legislators the urgency of addressing this public health crisis.

Data Summary

Before continuing to the final conclusions of this study, it is necessary to briefly summarize the main evidence and findings explained in-depth above. For decades, the agricultural industry has been using antibiotics for two main reasons: disease treatment and production purposes. Today, in the United States, 70% of all antibiotics used are for food-producing animals (Boris). That equates to nearly 28 million pounds of antibiotics annually (Boris). Because of the close-quarters animals are subject to on factory farms, disease spreads quickly. To combat this, low doses of antibiotics are provided through feed or water to prevent disease. This results in meat and food products contaminated with the same low doses of antibiotics, exposing human consumers (Boris). According to the CDC, one in five cases of resistant infections is the result food-borne pathogens like E. coli, and clearly cites the connection between agricultural antibiotic use and antibiotic resistance in humans. Sub-therapeutic doses in animal feed or water are used for production purposes of preventing disease and encouraging faster weight gain. The FDA, however, does not consider disease prevention as a production purpose, unlike countries in the European Union. The FDA seems to be caught in the middle, attempting to serve both public health and industry interests.

In 2013, the FDA unveiled GFI #213. The voluntary regulation's purpose was to decrease agricultural antibiotic use by relabeling medically important drugs from OTC to VFD or prescription only. However, there are significant weaknesses in the policy. First off, it is not legally binding, and operates only as a suggestion to pharmaceutical companies. These companies also disagree with the FDA over which drugs are considered medically important. Also, even though antibiotics now cannot be used for production purposes, the FDA considers sub-therapeutic dosages for disease prevention a therapeutic use. Veterinarian oversight is also

subjective when prescribing antibiotics. Finally, though there is a timeline for voluntarily adopting these measures. There is not a current plan in place for failures.

The FDA annual reports detailing antibiotic distribution highlight the current inefficacy of GFI #213. From 2009 through 2016, total antibiotic sales actually rose by 11%. Furthermore, even though GFI #213 specifically targeted reducing OTC consumption, as of 2016, 96% of all antimicrobials distributed were still categorized as OTC dispensing status. This marks only a 2% drop since 2013. The data itself is subject to questioning, due to the fact that drugs with production uses and therapeutic uses are grouped together, making it difficult to determine if there has been any decline in specific dispensing reasons. This is due to the preservation of business confidentiality, and demonstrates industry bias by the FDA.

Conversely, Denmark has a robust and proactive surveillance and policy system in place that has proved successful in eliminating non-therapeutic antibiotic use in agriculture, while decreasing the amounts of medically-important drugs overall. According to Hammerum et al, “Denmark was the first country to establish a systematic and continuous monitoring program of antimicrobial drug consumption and antimicrobial agent resistance in animals, food, and humans” (Hammerum et al). This comprehensive surveillance system is known as the Danish Integrated Antimicrobial Resistance Monitoring and Research Program (DANMAP), and continues to collect vital data used in epidemiological and public health research today through the Danish Central Husbandry Register (CHR). The CHR assigns each farm a number, and collects business and geographic data such as ownership, farm size, livestock type and number (“DANMAP 2016”). The FDA does not have the surveillance capabilities necessary to impose parameters of antibiotic use. Denmark’s complex plan of action includes strict mandatory components, which contrasts with the voluntary nature of FDA GFI #213. This holistic approach

reduced antibiotic overuse by addressing industry pressures, for example, the Danish government enacted regulations restricting profits that veterinarians could receive from drug sales.

Throughout the late 1990s, Denmark continued to monitor environmental antibiotic resistance and by 1999, eradicated all non-therapeutic antibiotic use in swine operations, which led to an increase of production from 18.4 million weaning pigs in 1992 to 27.1 million in 2008 (Levy).

The FDA foremost needs comprehensive, detailed, and accurate surveillance of agricultural antibiotic use, such as VetStat in Denmark, which collects data daily from pharmacies in order to accurately track antibiotic use in food-producing animals (“DANMAP 2016”). Knowing where, how, why, and what drugs are dispensed to food producing animals is essential in providing a strong scientific basis to target overuse and provide accurate data on which to base reduction policy efforts.

Further Conclusions

While voluntary change to how antibiotics are labelled and disseminated aids in surveillance, this only remedies the symptoms. The causes that drive the need for continued antibiotic use are the farm conditions and the economic push for low price and high quantity. By the end of 2018, the FDA will release the 2017 annual report, which marks the official end of the three-year voluntary adoption period. Perhaps the data will indicate a continuation of the 2015-2016 decrease in overall consumption, but will this be enough? Pharmaceuticals and industry will no doubt continue to resist regulation in court, proverbially tying the FDA’s hands. However, this delay could lead to a multi-drug resistant disease outbreak among humans. Unfortunately, it seems likely a disease emergence would be the double-edged sword necessary to targeting agricultural antibiotic abuse. There would finally be an undisputable direct link between animal resistance and subsequent human infection in the United States. Regardless of

what the future may bring, the time to act is now. First, the U.S. needs to emulate and create an adaptation of Denmark's multi-disciplinary approach to reducing non-therapeutic antibiotic use, and identifying current challenges. This includes detailed antibiotic use surveillance in humans and animals, and adopting strong enforcement policies, such as taxing antimicrobials used in agriculture, and providing subsidies for antibiotic alternatives ("Review"). Reacting in a meaningful way to continue to monitor and improve the AMR outlook for both humans and animals is absolutely vital. Antibiotic resistance is fundamentally a global health threat due to the ever-increasing interconnectedness of the world today. People, animals, and products are constantly crossing borders, bringing pathogens along with them. With growing amounts of resistance and limited options of treatment, slowing down the proliferation of antibiotic resistant pathogens is crucial to human, animal, and environmental health.

Notes on Methodology Reasoning and Research Technique Discussion

This study emphasized a multi-disciplinary methodology in order to underscore the facets involved in public health policy creation. The final structure of the paper reflects the main purpose—to highlight domestic policy strengths and weaknesses, and to improve proactive policy formation by adopting successful tactics used globally. FDA GFI #213, as a harbinger of FDA efforts to finally curb antibiotic overuse, acts as a case study. According to FDA GFI #213, FDA GFI #209 and VFD are to be used in conjunction with FDA GFI #213 as part of a joint plan to reduce and control medically important antibiotic use in livestock. Thus, FDA GFI #209 and the Veterinary Feed Directive (VFD) were used to determine similarities in structure as well as to demonstrate continuity among FDA regulation efforts. Additionally, this study identified select motivations of pharmaceutical corporations, agricultural associations, veterinary institutes, and public health organizations invested in the issue of agricultural antibiotic use that may have influenced the composition of FDA GFI #213. To ascertain these influences within FDA GFI #213's composition, this study reviewed documents from the CDC and WHO (mission statements and releases) that declare an aggressive stance and public health action plan for antibiotic resistance. Ultimately, this will help to provide further insight to the motivations and audience (both explicit and implicit) of FDA GFI #213, to gain a more accurate picture of the goals of the regulatory document and whether it acts in the best interest of public health.

Determining the effectiveness of voluntary regulations that FDA GFI #213 set forth had two parts—first, this study examined the benefits of voluntary regulation in general from a legal standpoint, then focused on the structure and capability of FDA GFI #213. To establish the strengths of voluntary regulation, the FDA's statements and studies justifying the FDA GFI #213 were examined, as well as a review of peer-reviewed journal articles about the health and

economic implications of FDA voluntary regulations. These journal articles provided additional perspectives on FDA regulatory techniques and the health consequences in regards to antibiotic resistance. A balanced view is necessary to discover relevant subtext within the issue and evidence that may need further research.

To research whether FDA GFI #213 led to a significant decrease in agricultural antibiotic use, this study examined antibiotic sales and usage amounts from the years of 2009 to 2016. The FDA's annual "Summary Report On Antimicrobials Sold or Distributed for Use in Food-Producing Animals" provided numerical data. This document listed the drug classifications, route of administration, dispensing status, estimates of drug use itemized by species, and provides multi-year trends on agricultural antibiotic use. By comparing antibiotic use with a timeline of before and after the release FDA GFI #213, this study reliably concluded the inefficacy of current FDA voluntary regulations.

Finally, this study compared domestic FDA regulation status with the widely successful policy strategies in Denmark. Differences in policy enforcement, data collection and sourcing, along with comprehensive surveillance techniques provided and integrated approach not only in comparing the United States with Denmark, but in piecing together a more cohesive and aggressive policy arrangement. In summation, this study concluded the FDA's Guidance for Industry #213 exemplifies how voluntary regulations do not have the ability to decrease antibiotic use in livestock, thus proving ineffective in combating the proliferation of antibiotic resistance. The balance between economic and public health concerns present in the structure of FDA GFI #213 influence the medical consequences of antibiotic resistance exposure for global human health. While FDA GFI #213 is foremost an agricultural policy issue, agricultural antibiotic contamination in the environment and subsequent antibiotic resistant infections are a

threat to human health. This methodology is only one of many different approaches to evaluating policy efforts, each just as important when investigating such a vast yet vital crisis.

However, there are contingencies to account for in this methodology. In recent years, the FDA has improved surveillance techniques of antibiotic resistance such as the National Antimicrobial Resistance Monitoring System (NARMS), as well as documentation of antibiotic use in agriculture, such as the USDA's National Animal Health Monitoring System (NAHMS). Perhaps this improvement in accuracy accounts for an apparent rise in antibiotic use. These methods of surveillance have notable limitations regarding data reporting in order to protect confidential business information. In recognition of this, the thesis noted both antibiotic resistance monitoring systems and their weaknesses. There may be other factors that contribute to an increase in agricultural antibiotic use, such as USDA regulations regarding livestock operation conditions and other environmental factors. In addition, the comparison of Danish policies is not meant to act as a default example of success, owing to the fact that the Danish legislative process, confidentiality rights, and agricultural industry operates under different structures. These points were taken into consideration while conducting research and forming conclusions.

Keywords

For the sake of clarity and consistency in analyzing policy, significant technical terms central to FDA GFI #213 must be defined. The wording of the document contains essential terms with specific FDA definitions vital to understanding the purpose and regulatory meaning given to suggestions listed for drug sponsors. Without a shared understanding of the official FDA meaning of terms like judicious use of antibiotics, antibiotics important to human health, and non-therapeutic use, there could be conflicts regarding the goals and methods of FDA GFI #213, as different groups (such as CDC or National Pork Producers) may give different meaning to those terms. This will be reflected in the study of the language used within FDA GFI #213, relating to enforcement issues and economic preference. Thus, for uniformity, this study uses definitions provided by the FDA. Antibiotic resistance: a subsection within antimicrobial resistance, defined as when bacteria become immune to a drug after exposure.

Central Husbandry Register (CHR): This is a register of all Danish farms defined as geographical sites housing production animals. It contains information concerning ownership, farm size, animal species, age groups, number of animals and production type. Each farm has a unique farm identity number (CHR-number).

Concentrated Animal Feeding Operation (CAFO): a large animal feeding operation where a large population of animals are raised within a small land area. Population size varies by species and can be found at:

<https://www.nrcs.usda.gov/wps/portal/nrcs/main/national/plantsanimals/livestock/afo/>

Document/Regulation: refers to interchangeable names referring to GFI #213, may also include “regulatory document.”

Food-producing animals: includes any animal either directly consumed or whose bi-products are consumed.

Judicious use: The use of medically important antimicrobial drugs in food-producing animals “should be limited to those uses that are considered necessary for assuring animal health,” and “should be limited to those uses that include veterinary oversight or consultation.”

Medically important antibiotics: directly cites the full list of drugs found in FDA GFI #209 Appendix A that are vital in treating human disease. This list is not static and is subject to change with the introduction of new drugs and current disease outbreaks.

National Animal Health Monitoring System (NAHMS): USDA surveillance program that monitors the health and health management of domestic livestock populations

Non-therapeutic antibiotic use: is interchangeable with the FDA term “production purposes,” which refers to, “the use of antibiotics with the intent of enhancing growth or improving feed efficiency.”

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